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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARC PREAUDAT, CHIKASHI TOKUDA,
and LAURENCE JACQUEMART

Appeal 2009-012075
Application 10/522,909
Technology Center 1600

Oral Hearing Held: June 24, 2010

Before ERIC B. GRIMES, DEMETRA J. MILLS, and
MELANIE L. McCOLLUM, Administrative Patent Judges.

On Behalf of the Appellants:

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The above-entitled matter came on for hearing on Thursday, June 25, 2010, commencing at 9:00 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, 9th Floor, Hearing Room A, Alexandria, Virginia, before Jan M. Jablonsky, court reporter.

THE USHER: Appeal Number 2009-012075, Mr. KC.

JUDGE GRIMES: Good morning, Mr. KC.

MR. KC: Good morning, Your Honor.

JUDGE GRIMES: Before you get started, if you would not mind introducing your guest for the record, and if you have a business card, the court reporter would appreciate it.

MR. KC: I did not bring a business card along with me.

JUDGE GRIMES: And if you wouldn't mind introducing your guest for the record?

MR. KC: Sure. My name is Sagun KC. I'm with Millen, White, Zelano & Branigan, and with me is Diana Hamlet-Cox. She is an attorney at Millen, White, Zelano & Branigan, as well. And we're here on behalf of our client, Mark Preaudat, et al. And the assignee of record, which is CIS Bio International.

This is Appeal Number 2009-012075 in relation to certain claims of this application which have been rejected under 103(a) as allegedly being obvious in view of two references. The first reference is by Bazin et al. in Spectrochimica Acta. And the second reference is United States Patent to Nicolson, et al.

The claims of this application are directed to a method for measuring endoglycosidase activity comprising employing a substrate, which is cleaved by endoglycosidase. The steps are you contact a sample

containing the endoglycosidase with the substrate and the substrate has two moieties attached to it: a donor moiety and an acceptor moiety; and you're measuring the amount of intact substrate by monitoring the reduction in the energy between the transfer of energy between the donor and the acceptor molecules.

So if I may read the claim, it's a method for determining endoglycosidase enzyme activity in a sample comprising bringing a substrate which can be cleaved by said endoglycosidase into contact with said sample and measuring the change in the amount of intact substrate. The decrease in the amount of substrate being representative of the endoglycosidase activity, and the substrate is directly or indirectly bound with a donor compound and an acceptor compound, and the amount of intact substrate is measured by measuring the signal emitted by the acceptor compound.

The signal is usually because of a change of a transfer via a close proximity between the donor and the acceptor molecules. The Examiner relies on two references, as I mentioned earlier. The first primary reference is by Bazin et al., and Bazin is concerned with the methods of measuring protease enzyme activity. Proteases as we know are different from endoglycosidase in terms of the substrates that they act on.

Proteases by definition act on proteins. Endoglycosidases act on glycosidic linkages or sugar molecules. So the macromolecular structure is different. On one end we have sugar molecules, and the other end we have protein molecules. And in Bazin et al, they basically describe fluorescence, resonance, energy transfer, or the threat process between one during a compound. In this case it's a cryptate which has a rare earth metal

bound to it which can transfer energy to an accepted molecule, and in this case it's an allophycocyanin and you're basically measuring a cleavage of the protein by the action of a protease. The secondary reference that the Examiner --

JUDGE GRIMES: The assay that's used in the Bazin reference, that is one that meets the limitation in your claim. Correct? You've got the signal emitted by the acceptor compound?

MR. KC: Yes, yes. That's correct, Your Honor.

JUDGE GRIMES: It's just the different substrate being included?

MR. KC: Right. Right. It's a different substrate being included and the secondary reference that the Examiner relies on is a method for measuring endoglycosidase activity using a substrate Heparin Sulfate in this case, which is cleaved by endoglycosidase. But the method relies on measurement of fluorescence. There is no energy transfer process going on between any of these moieties that are recited in our claims, and the method employed by the secondary reference, Nicolson, relies on chromatographic separation or resolution of the moiety that's cleaved through the action of endoglycosidase.

So the Applicant's position in this case is that a combination of Bazin and Nicolson fail to teach each and every element of the claimed process. Also, there are certain secondary considerations that I wish to mention here .

JUDGE GRIMES: Before you get into the secondary considerations, why would it not be obvious to apply the fret assay from Bazin to the substrate that's used in Nicolson?

MR. KC: Okay. The answer is in Bazin they use a peptide moiety that is cleaved, but is attached on one end. It's attached to a donor compound. On the second end it's attached to an acceptor compound. The peptide structure in comparison to Heparin sulfate, which is a substrate, one of the substantive examples of a substrate used in that application is very simple in that if you look at the amino acid sequence you can derivitize the N terminus or the C terminus. Okay.

So, basically, what the N terminus is derivitized with an acceptor of a donor compound, the C terminus is derivitized with an acceptor compound. So there is only a certain number of possibilities, possible structures that can be made for this process. In our case it's a sugar moiety; and, if you look at the simplest structure with is a heparin sulfate structure, it contains glycosamineglycan and that's glycosaminine. So the two compounds have at least six possible structural positions that you can derivitize. That's one part.

JUDGE GRIMES: Are you saying you wouldn't be able to limit the donor accept the fluorescence donor to one end and the fluorescence acceptor to the other end.

MR. KC: Yes, there are two considerations. One is that the enzyme, the donor and acceptor molecules have to be in sufficient proximity to allow energy transfer between the two moieties. And the secondary consideration is that well, you need sufficient proximity, but it cannot be in such proximity that the enzyme that acts on it is directly hindered, if I may. So those are the two considerations that you need to take into account.

And, unfortunately, the primary reference since it does not disclose any sugar molecules whatsoever, there's a broad disclosure of how

this technique can be applied for protein producing actions for binding to RNA polymerases, study of those macromolecules, but does not teach or suggest any sugar containing compounds. And that is the fundamental difference between the present claim of the invention and the primary reference.

The secondary reference does not rectify any of the limitations, because as I discussed earlier it is using a simplistic chromatographic separation and does not allow or does not each or suggest the resonance, energy transfer between that. So it does not teach or suggest any of the active method steps that I recited in the claims.

JUDGE GRIMES: You alluded to some secondary considerations?

MR. KC: Yeah. Secondary considerations as I mentioned earlier, Your Honor, you can look at the structure of the simplest molecule, the substantive molecule, heparin sulfate. It is a polysaccharide that has repeat chains of N-acetylglucosamine linked to D-glucuronic acid. So you can have five possible secondary modifications. One is the epimerization of one of the carbons to yield 20 different secondary structures.

The second is you can have sulfano moieties attached to the hydroxyl groups off the carbon atoms in the sugar so that there is a different secondary structure. So if you have a disaccharide owing to these five possible permutations it leads to 32 different combinations. So a heparin solvent molecule just containing two sugar residues would theoretically have in a chain up to a million possible structures. So the structure and complexity of the substrate in question is more diverse, more variable than the substrates that I described by the cited prior art references.

That's my first point, and in order to support that position, we've submitted this reference by Codee, which raises Applicant's position that the heparin sulfate molecule is highly complex. It has different micro heterogeneous secondary structures, and the resulting effect is that it is virtually impossible to obtain specific heparin sulfate from natural sources. And, lastly, I also wanted to mention is that one skilled in the art would have appreciated the difference between the assays in question, which is heparinase compared to the prior art teachings of protease assays and would have instantly recognized that a protease assay is insufficient or does not cater towards measurement of endoglycosidase activity.

JUDGE MCCOLLUM: Can you point me to any place in the specification that might give me some guidance as to what the inventors had to do to overcome the complexity issue? Like what did they have to do differently? Does the specification talk about anything that they had to do differently to make this work with this different substrate rather than the peptide?

MR. KC: Right. If I remember correctly there's another discussion with respect to measurement of heparinase activity and the existing technologies that rely on chromatographic gelatin preparesus and the like, but as far as the peptide substrates are concerned, I don't know if there is explicit guidance in the specification, so. I mean in order to read my position the prior art teachings have heparin sulfate tethered to a substrate and you're measuring the lysed moiety of the lysed sugar residue in heparin sulfate by chromatographic volution or gelatin preparesus so that you can see a side migration. But it does not teach or suggest a sensitive assay technique which can be using a Heitwood format for example and does not

require separation of the lysed moiety through a FRET-based analytical technique.

JUDGE MILLS: Isn't it well-known to those of ordinary skill in the art the substrates on which endoglycosidases act and we have a teaching in the Bazin reference saying that the distance for energy efficient transfer between molecules using the fret assay in the one to seven nanomole range?

MR. KC: Correct.

JUDGE MILLS: Don't we have general teachings that would guide one of ordinary skill in the art here?

MR. KC: Right. If I may, is that nanomole or nanometers? I believe that this sense --

JUDGE GRIMES: Nanometer, yes. Maybe it's nanometer, yes.

MR. KC: Yes, you are absolutely right. The distance is, the fret assay is based on really, real close proximity between the donor and the accepted compounds. If you're using a peptide fib in a peptide format, let's say you have a secondary structure prediction that allows you to tether these donor and accepted compounds so that you would have energy transferred between them. So its more predictable secondary structure so that you can engineer, you know.

We had these donor and acceptor molecules designed so that you can have the fret transfer. In our case in the sugar molecule, it's more level, if I may. The second structure is not as rigid, so there's more difficulty of predicting where the donor and the acceptor compounds reside.

JUDGE GRIMES: Do you have anything else to add?

MR. KC: I think that's it, Your Honor.

The hearing was concluded at 9:20 a.m.